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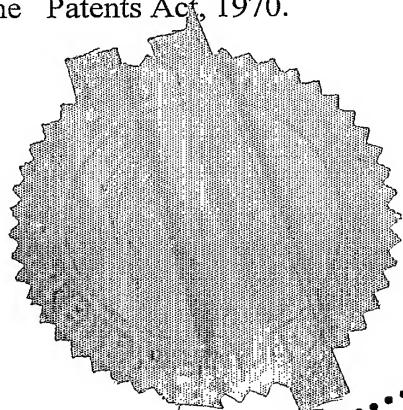
तोडी इस्टेट, 3 री मंजिल, सन मिल कंपाउंड, लोअर परेल (प.), मुंबई - 13  
Todi Estate, 3<sup>rd</sup> Floor, Sun Mill Compound  
Lower Parel (West), Mumbai – 400 013

**दूरभाष Tel** ☎ 022-2492 4058  
 022-2492 5092  
 022-2496 1370  
 022-24949845  
 022-24922 / :0  
**फॅक्स Fax** ☎ 022-2495 0622  
 022-24903852  
**Email** patmum@vsnl.net  
**Website** www.ipindia.nic.in

## **THE PATENTS ACT, 1970**

IT IS HEREBY CERTIFIED THAT, the annex is a true copy of the Application and  
Provisional Specification filed on 07/10/2004 in respect of Patent Application No.1058/MUM/2004 of **SUN**  
**PHARMACEUTICAL INDUSTRIES LTD., ACME PLAZA ANDHERI-KURLA ROAD,**  
**ANDHERI (E), MUMBAI – 400 059, MAHARASHTRA, INDIA, AN INDIAN COMPANY.**

This certificate is issued under the powers vested in me under Section 147 (1) of the Patents Act, 1970.



Dated this 25<sup>th</sup> day of July 2005.



**(RAKESH KUMAR)**  
**ASSTT.CONTROLLER OF PATENTS & DESIGNS.**

FORM 1

THE PATENTS ACT, 1970  
(39 OF 1970)

APPLICATION FOR GRANT OF A PATENT  
(See sections 5(2), 7, 54 and 135 and rule 33A)

We, SUN PHARMACEUTICAL INDUSTRIES LTD., ACME PLAZA, ANDHERI-KURLA ROAD, ANDHERI (E), MUMBAI-400059, MAHARASHTRA, INDIA

AN INDIAN COMPANY

hereby declare -

- (i) that we are in possession of an invention titled "**GASTRIC RETENTION DRUG DELIVERY SYSTEM**".
- (ii) that the provisional specification relating to this invention is filed with this application.
- (iii) that there is no lawful ground of objection to the grant of a patent to us.

We, further declare that the inventors for the said invention are

(1) DHARMADHIKARI, Nitin Bhalachandra; (2) ZALA, Yashoraj Rupsinh; both of SUN PHARMACEUTICAL INDUSTRIES LIMITED, 17/B Mahal Industrial Estate Off Mahakali Caves Road, Andheri (E), Mumbai 400093, Maharashtra, India; all Indian nationals.

We claim the priority from the applications filed in convention countries, particulars of which are as follows: Not Applicable

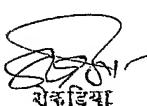
We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which we are the applicant: Not Applicable

We state that the application is divided out of our application, the particular of which are given below and pray that this application deemed to have been filed under section 16 of the Act: Not Applicable

That we are the assignee of the true and first inventors.

That our address for service in India is as follows-

Dr. RATNESH SHRIVASTAVA,  
INTELLECTUAL PROPERTY CELL,  
SUN PHARMACEUTICAL INDUSTRIES LTD,  
17/B MAHAL INDUSTRIAL ESTATE  
OFF MAHAKALI CAVES ROAD, ANDHERI (E),  
MUMBAI 400093, MAHARASHTRA, INDIA.  
TEL : 56455645, FACSIMILE 56455685

300/ इथे मकान/स्टेट नं. 300 अंडेरी कुर्ला  
CBR संख्या 10380 7/10/04  
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सना. अधिकारी

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1058/mum/2004  
Dtd 7/10/2004

Following declaration was given by the inventors-  
We, the true and first inventors for this invention declare that the applicant herein is our assignee.

Dated this 7<sup>th</sup> day of OCTOBER , 2004

(Signatures) 1. N.B.Dharmadhikari  
DHARMADHIKARI, Nitin Bhalachandra

2. Yashoraj  
ZALA, Yashoraj Rupsinh

That to the best of our knowledge, information and belief, the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of a patent to us on this application.

Following are the attachment with the application:

- 1) Provisional specification (3 copies)
- 2) Fee Rs. 3000 in cheque bearing No. 002224 dated Sep 8, 2004 drawn on Kotak Mahindra Bank.

We request that a patent may be granted to us for the said invention

Dated this 7<sup>th</sup> day of OCTOBER , 2004.

(Signature) .....  
DILIP SHANGHVI  
DILIP SHANGHVI  
CHAIRMAN AND MANAGING DIRECTOR  
SUN PHARMACEUTICAL INDUSTRIES LTD.

To

The Controller of Patents,  
The Patent Office,  
Mumbai - 400 013.

FORM 2

THE PATENTS ACT, 1970  
(39 OF 1970)

PROVISIONAL SPECIFICATION  
(See section 10)

GASTRIC RETENTION DRUG DELIVERY SYSTEM

SUN PHARMACEUTICAL INDUSTRIES LTD.

A company incorporated under the laws of India having their office at ACME PLAZA,  
ANDHERI-KURLA ROAD, ANDHERI (E), MUMBAI-400059, MAHARASHTRA, INDIA.

The following specification describes the nature of this invention.

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ORIGINAL

## **GASTRIC RETENTION DRUG DELIVERY SYSTEM**

The present invention relates to a novel gastric retention drug delivery system in the form of a tablet or a capsule coated with an expandable coating, more particularly, with an expandable coating comprising a film-forming polymer and an expandable component.

### **BACKGROUND OF THE INVENTION**

Controlled drug delivery systems deliver drug to the body so as to establish therapeutically effective blood levels of the active ingredient and once these blood levels are achieved they continue to maintain constant blood levels for long durations by delivering the drug to the body at the same rate as the body eliminates the drug. By avoiding peaks and troughs in blood levels associated with conventional dosage forms, controlled drug delivery systems lower the incidence of adverse effects or side effects. Very importantly controlled drug delivery systems reduce the frequency of dosing leading to convenience to the patient in terms of dosing and compliance to the specified dosage regimens.

It is generally known that the rate at which an oral controlled drug delivery system delivers the drug into the blood is not the same as the rate at which it releases the drug into a test aqueous fluid because the gastrointestinal fluid's pH, composition and agitation intensity change with the specific location of the drug delivery system in the gastrointestinal tract i.e. from the stomach to the colon, fasted versus fed state, type and amount of food ingested, and also vary from individual to individual. In addition, the drug may not be absorbed in the same manner and propensity as we move from the stomach to the colon. Some drugs have an "absorption window" i.e. they are absorbed only from the upper parts of the gastrointestinal tract, whereas there are others whose absorption from the colon is not uniform or complete. Thus, the location of the controlled drug delivery system in the gastrointestinal tract as well as the rate at which the controlled drug delivery system moves from the stomach to the colon represent important factors that need to be considered in the design of an oral controlled drug delivery system. It is thus known to those skilled in the art that an oral controlled delivery should be designed not only with a control on the rate at which it releases the drug over the drug delivery time period (temporal control) but also a control on the location from which it is delivered (spatial control). The spatial control can be achieved by prolonging the period of retention of the system in the stomach. Gastric retention systems are also beneficial when the drug is effective locally in the stomach. Drugs absorbed in the upper part of the gastrointestinal tract may exhibit variability in absorption due to inter and

intra-individual variability in gastric emptying and gastrointestinal motility. This variation in absorption may be addressed by administering a dosage form comprising the drug such that a small part of the drug is available as immediate release, and a large part is available as sustained or controlled release.

One of the approaches that has been used for achieving spatial control involves increasing the gastric retention of sustained or controlled drug delivery systems by using a composition containing highly swellable polymers in admixture with a gas-generating agent to form systems that are large in size as well as capable of floating on gastric fluids. It has now become well recognized by those particularly skilled in the art that systems containing swellable polymers will instantly float on gastric fluids because the gas generated and entrapped within the system decreases the density. Swelling to a large size is an important factor in gastric retention of the system. Solids having a size less than 5 to 7 mm show delayed gastric emptying in fed conditions but they can still be emptied from the stomach because their size is smaller than the pyloric sphincter. Even floating systems of size less than 5 to 7 mm can be emptied if the patient is in supine position. The mean resting pyloric diameter is approx. 13 + 7 mm and it has been reported that dosage forms with a size of approx. 12-18 mm diameter in their expanded state would generally be excluded from the passage of the pyloric sphincter. The system should also be capable of retaining this size in the gastric fluids for long periods under agitational conditions created by gastric motility. Such large intact systems cannot be emptied until the arrival of the interdigestive migrating motor complex at the beginning of the interdigestive phase. The combination of increase in size and floatation results in increased gastric retention of the system. The prior art resulting in this current state of the art is described below.

(A) Swellable gastric retention floating matrix drug delivery systems :

The term "swellable gastric retention drug delivery system" herein refers to systems that are not coated with a polymer coating or not placed inside a polymer envelope or a pouch. Representative prior art illustrating the development of this type of systems is described below.

United States Patent No. 4,777,033 ('033 patent, priority date June 11, 1985) assigned to Teijin Limited, discloses an oral sustained release pharmaceutical preparation comprising a lower alkyl ether of cellulose, polyacrylic acid or its pharmaceutically acceptable salt, a drug, and an effective amount of effervescent foaming agent. Tablets made from the composition however still retained major disadvantages in that the tablets did not remain intact when subjected to dissolution testing.

The disintegrated tablet thus does not attain or maintain a size suitable for long duration of retention in the stomach. This prior art presented the problem that if a large amount of gas generating agent, such as sodium bicarbonate, is used in order to sufficiently reduce density and maintain the lowered density for sufficient length of time for achieving floatation of the system, then tablets formed from the same disintegrate.

United States Patent No. 5,651,985 ('985 patent, priority date Feb 28, 1994) assigned to Bayer AG, claims a pharmacologically active composition comprising a pharmacologically active compound dispersed in a homogenous mixture on the molecular level of polyvinylpyrrolidone and a methacrylic acid polymer having an acidic number between 100 and 1,200 mg of KOH/g of polymer solid substance, and optionally a gas-forming additive. With the use of gas-forming additive, the density of the system was reduced on gas generation and the systems were capable of floatation in aqueous medium. The tablets did not disintegrate in an aqueous medium and exhibited marked swelling and high dimensional stability in the swollen state. This dimensional stability was attributed to the non-erodible matrix used in the system. However, the system used relatively low quantities of gas generating agent relative to the '033 patent, and it is not known if the dimensional stability of the system can be maintained when higher quantities of the gas generating additive are used.

United States patent number 5,783,212 ('212 patent, priority date Feb 2, 1996) assigned to Temple University claims a controlled release pharmaceutical tablet comprising a first barrier layer comprising a first swellable, erodible polymer, a drug layer comprising a second swellable, erodible polymer, and a second barrier layer comprising a third swellable, erodible polymer, wherein said first and second barrier layers are adapted to swell and to erode faster than said drug layer; said faster swellability and erodibility of said first and third layers adapted to increase drug delivery from the onset of dissolution. The patent also covers systems wherein at least one of said layers includes a gas-evolving material, which helps the system to float and increases the time of retention of the tablet in the stomach. The patent includes examples wherein the multilayered tablets are obtained by compression and the gas-evolving layer contained relatively larger quantity of the gas-generating agent. All tablets were found to float within about 15 minutes. The examples used polyethylene oxide (PEO) as polymer. Whereas the PEO could retain larger quantity of gas generated by the larger amount of gas generating agent used, the limitation was that the patent exemplified only one polymer that could do so.

United States patent number 6,261,601 ('601 patent, priority date Sep 17, 1997) assigned to Ranbaxy Laboratories used superdisintegrants in the composition. Superdisintegrants are known to swell to several times their volume, their swellability being superior to conventional hydrogel forming swellable polymers such as those used in the '033 patent. The pharmaceutical composition claimed in the patent comprises a drug, a gas-generating component, a swelling agent, a viscolyzing agent, and optionally a gel-forming polymer. The gas generating agents used were carbonates or bicarbonates. The system used viscolyzing agents to prevent disintegration of the system. The drawback of the system was that in order to prevent disintegration of the system, the amounts of superdisintegrant, viscolyzing agent and gas generating agent were required to be optimized. Simultaneously, it was also required that the amounts of excipients be such that the system acquires buoyancy immediately, attains a large expanded size immediately and maintains these characters for sufficient time over which gastric retention is desired. Achieving all these objectives simultaneously is difficult and the formulator may not always be able to do so. Further, the gellable matrix forms an erodible layer on the surface, whereas the core remains dry. Thus, not all of the gas generating agent in the system reacts with the acid of the system. Hence, the buoyancy of the system is capable of being improved by formulating systems where a significant amount of gas generating agent can react with the acid of the environment.

Other prior art references that utilized swellable gastric retention floatation matrix drug delivery systems include WO 0110419A1, WO 0023045A1, WO 0110417A1 and WO 03011255A1.

(B) Gas generating composition in an expandable polymer envelope or pouch :

United States patent number 3,786,813 ('813 patent, priority date Dec 27, 1972) assigned to Alza Corporation, claims a drug delivery device for the controlled and continuous administration of a drug to an environment of use comprising a hollow expandable closed member having therein self-contained means for expandable the member, the member being affixed to drug delivery means for delivering a drug at a controlled rate over the given period of time. The patent exemplifies systems wherein a gas generating compartment is connected to a balloon such that the gas generated upon contact with the gastric environment causes the balloon to expand, thereby causing the system to float.

United States patent number 4,207,890 ('890 patent, priority date Jan 4, 1977) assigned to McNeilab, claims a drug dispensing device for controlled and prolonged internal administration of a drug comprising (a) a collapsed, expandable, imperforate envelope made of a substantially

non-hydratable, body fluid permeable, drug-permeable polymer film; (b) drug metering means containing said drug and retained by said polymer envelope, whereby drug is dispensed at a predetermined rate; and (c) an effective expandable amount of an expandable agent contained within said polymer envelope, the combination of which agent and which drug when in contact with body fluids cause said polymer envelope to expand to a volume such that the device is retained in the environment of use for at least the minimum desired time. The patent claims systems wherein the polymer film is not applied directly onto the surface of the drug-containing core, but is present in the form of an envelope.

United States patent number 4,996,058 ('058 patent, priority date Sep 18, 1987) assigned to Ciba-Geigy Corporation relates to a dosage form consisting of a sachet which is film coated or filled into capsules, the sachet containing a component that expands on contact with gastric juice and an agent capable of releasing carbon dioxide or nitrogen. The patent does not disclose an expandable coating formed by coating a composition comprising a film forming polymer and an expandable component on the surface of a tablet or capsule core, or a method for coating such a composition on the surface of a tablet or capsule core. We have found that coatings using film forming polymer alone when coated on to tablet or capsule cores of the present invention do not provide desirable floatation, swelling and/or integrity of the system.

United States patent number 6,290,989 ('989 patent, priority date Jan 14, 1997) assigned to LTS Lohmann Therapie-Systeme AG, claims device for the controlled release of active compounds in the gastrointestinal tract with delayed pyloric passage, which device is an improvement over the device of the '890 and '058 patents. The '890 and '058 patents did not provide advice on how the release rate of active compound is to be controlled independently of the permeability of the polymer forming the sachet. The '989 patent teaches that the active compound can be incorporated in the form of multiparticulates whose nature and composition provides for means for controlling the rate of release of the active compound. Multiparticulates could be present inside the sachet or embedded in the film forming the sachet.

PCT publication number WO 9959637 ('637 patent, priority date May 18, 1998) assigned to LTS Lohmann Therapie-Systeme AG, relates to a device for the controlled release of active agents in the gastrointestinal tract with a prolonged pylorus passage in the form of a bag which expands when the gas generating component of the system generates gas upon contact with gastric juice. The bag is constructed with a polymer membrane made of a monolayered film which controls the

release of an active agent located therein, and thus the system has the drawbacks associated with the systems of the '890 and '058 patents.

United States patent number 6,776,999 ('999 patent, priority date Oct 30, 1998) assigned to LTS Lohmann Therapie-Systeme AG, claims a swallowable, gastroretentive device, which delays passage of the device through the pylorus of the stomach of an orally ingestible pharmaceutical form and releases at least one pharmaceutically active compound in a controlled manner, said device comprising: (a) a pharmaceutical form which contains at least one pharmaceutically active compound; (b) an expandable component which generates gas on contact with gastric juice; and (c) a polymeric membrane system which totally encompasses components (a) and (b) above and is expandable by the gas generated by (b) upon contact with the gastric juice, whereby the polymeric membrane system comprises at least one member selected from the group consisting of a microporous membrane, a porous membrane and a combination of any of the foregoing with a non-porous polymer film. The patent teaches a device in the form of a sachet, which for the purposes of facilitating administration and handling, can be filled into a container made of physiologically acceptable material, for example into hard gelatin capsules.

PCT publication number WO 04032906A1 ('906 patent, priority date Oct 11, 2002) assigned to DepoMed Development Limited, claims a gastro-retentive dosage form of levodopa for oral administration to a patient in need thereof, said dosage form comprising (a) a tablet comprising a therapeutically effective amount of levodopa, a binder, and a pharmaceutically-acceptable gas-generating agent capable of releasing carbon dioxide upon contact with gastric juice, and (b) an expandable, hydrophilic, water-permeable and substantially gas-impermeable, membrane surrounding the tablet, wherein the membrane expands as a result of the release of carbon dioxide from the gas-generating agent upon contact with the gastric juice, whereby the dosage form becomes too large to pass into the patient's pyloric sphincter. Although the application claims systems wherein the drug-containing core tablet is covered by an expandable, gas-impermeable membrane, the description and examples include systems wherein the drug-containing tablet is introduced into a sachet or pouch made of an expandable, gas-impermeable polyvinyl alcohol membrane. The patent application does not disclose an expandable coating formed by coating a composition comprising a film forming polymer and an expandable component on the surface of a tablet or capsule core, or a method for coating such a composition on the surface of a tablet or capsule core.

(C) Gas generating composition coated with polymer film :

United States Patent No. 4,101,650 ('650 patent, priority date Apr 6, 1977) assigned to Zaidan Hojin Biseibutsu Kagaku Kenkyu Kai discloses a formulation in which granules containing sodium bicarbonate, lactose and polyvinylpyrrolidone are coated with a layer of hydroxypropyl methylcellulose. These are then further coated with a suspension containing the active ingredient pepstatin and hydroxypropyl methylcellulose to form floating minicapsules of a diameter in the range of 0.1 to 2 mm. The drawback of this system is that the minicapsules are much smaller in size than required for long durations of retention in the stomach. Further, the hydroxypropyl methylcellulose layer on the granules is not an expandable polymer film but a film that gels on contact with an aqueous medium.

United States Patent No. 4,844,905 ('905 patent, priority date Feb 24, 1986) assigned to Eisai Co. discloses granules comprising a drug containing core; a middle gas-generating layer comprising sodium carbonate and organic acid; and an outer coat of an expandable polymer film. Although intended for remaining in the stomach, the granules have the disadvantage of small size. Whereas the coating on the granules works to provide floating granules, we found that when these coatings were used on a tablet or capsule core, the system did not float and the coating disintegrated.

United States patent number 6,284,271 ('271 patent, priority date July 1, 1997) assigned to Astrazeneca AB, claims an effervescent dosage form comprising, as a first component, effervescent excipients and as a separate second component, a plurality of individual units comprising a pharmaceutically active compound and optionally pharmaceutically acceptable excipients wherein each unit is provided with a floating generating system comprising at least two coating layers, one of which is a gas generating layer and the other layer is a barrier layer enclosing the generated gas, and wherein the first component is separated from the second component by the layers of the floating generating system. The patent exemplifies dosage forms wherein pellets comprising a core comprising the active ingredient were coated with an inner gas generating layer and an outer hydrophobic polymer layer, followed by mixing of the coated pellets with effervescent excipients and compression into a tablet dosage form. The patent does not disclose an expandable coating formed by coating a composition comprising a film forming polymer and an expandable component on the surface of a tablet or capsule core, or a method for coating such a composition on the surface of a tablet or capsule core.

None of the prior arts described above disclose or teach a gastric retention drug delivery system wherein a tablet or a capsule core is coated with an expandable coating, or teach a method of preparing such a system using suitable coating compositions. We have surprisingly found systems wherein a tablet or capsule core comprising an agent capable of generating internal pressure are coated with a coating composition comprising a film-forming polymer and one or more expandable components, such that most or all of the following desirable objectives are achieved simultaneously :

- the coating allows rapid permeation of water into the core to activate the agent capable of generating internal pressure on the coat
- the core and coat are both capable of expansion
- either the core or the coat or both may be formulated so as to control the rate of the therapeutically active agent
- the system rapidly achieves both buoyancy and a high degree of swelling
- the coating maintains its physical integrity in contrast to known film-forming compositions which may burst or rupture upon generation of internal pressure
- the coating maintains the original shape of the device upon expansion
- the system may be designed to provide the therapeutically active agent in immediate release form and in modified release form.

One system of the present invention may be defined as follows:

A gastric retention drug delivery system in the form of a coated tablet comprising :

- (a) a core in the form of a tablet comprising an agent capable of generating internal pressure on the coat, and
- (b) an expandable coating formed by coating a composition comprising a film-forming polymer and one or more expandable components on the tablet core.

The system is capable of achieving floatation rapidly and is expandable to a size suitable for retention of the system in the stomach.

Another system of the present invention may be defined as follows:

A gastric retention drug delivery system in the form of a coated capsule, comprising :

- (a) a core in the form of a capsule, the core comprising an agent capable of generating internal pressure on the coating, and
- (b) an expandable coating formed by coating a composition comprising a film-forming polymer and one or more expandable components on the capsule core.

The system is capable of achieving simultaneously the dual desirable properties of instantaneous floatation and expandability to a size suitable for retention of the system in the stomach.

The gastric retention drug delivery system of the present invention is useful in providing improved delivery of the therapeutically active agent. The therapeutically active agents that may be used in the gastric retention drug delivery system of the present invention may be selected from the following, viz. alcohol abuse preparations, drugs used for alzheimer's disease, anaesthetics, acromegaly agents, analgesics, antiasthmatics, anticancer agents, anticoagulants and antithrombotic agents, anticonvulsants, antidiabetics antiemetics, antiglaucoma, antihistamines, anti-infective agents, antiparkinsons, antiplatelet agents, antirheumatic agents, antispasmodics and anticholinergic agents, antitussives, carbonic anhydrase inhibitors, cardiovascular agents, cholinesterase inhibitors, treatment of CNS disorders, CNS stimulants, contraceptives, cystic fibrosis management, dopamine receptor agonists, endometriosis management, erectile dysfunction therapy, fertility agents, gastrointestinal agents, immunomodulators and immunosuppressives, memory enhancers, migraine preparations, muscle relaxants, nucleoside analogues, osteoporosis management, parasympathomimetics, prostaglandins, psychotherapeutic agents, sedatives, hypnotics and tranquilizers, drugs used for skin ailments, steroids and hormones. The gastric retention drug delivery system of the present invention may be prepared without the therapeutically active agent. Such a system is capable of swelling and being retained in the gastric environment. It gives a filling effect, thereby reducing the appetite and thus is useful in control of obesity.

The core of the gastric retention drug delivery system of the present invention includes an agent capable of generating internal pressure. The agent generating internal pressure may be selected from gas generating agents, one or more highly swellable polymers, superdisintegrants and mixtures thereof. The gas generating agent used in the core of the gastric retention drug delivery system of the present invention may include a single component that generates gas upon contact with the gastric fluid, or may include a gas generating couple. Gas generating components that may be used in the present invention include solids that liberate gas, especially carbon dioxide or nitrogen, for example under the action of body fluid or the hydrogen ions present therein. Examples include carbonates such as calcium carbonate, bicarbonates such as sodium or potassium bicarbonate, sulfites such as sodium sulfite, sodium bisulfite, or sodium metabisulfite, and the like, ammonium cations or sodium azide or mixtures thereof. These salts may be used alone or in combination with an acid source as a gas generating couple. The acid source may be

an edible organic acid, a salt of an edible organic acid, or mixtures thereof. Examples of organic acids that may be used include citric acid, malic acid, succinic acid, tartaric acid, fumaric acid, maleic acid, ascorbic acid, glutamic acid, alginic acid, acrylic acid and their salts, and mixtures thereof. Sodium bicarbonate is used as the preferred gas generating agent. The organic acid may also be a polymer, for example acrylic acid polymers and copolymers such as acrylate polymers available under the tradenames Carbopol®, Eudragit® L-100-55, Eudragit® S-100, Noveon® AA1, which react with carbonates or bicarbonates of alkali or alkali earth metal compounds to generate gas. These are generally used as auxiliary acid sources and may also have properties of themselves generating internal pressure by swelling when in contact with an aqueous medium. The gas generating agent is used in an amount ranging from about 0.5% to about 50% by weight of the core. Examples of highly swellable polymers that may be used in the present invention as agent capable of generating internal pressure include, but are not limited to, high molecular weight polyethylene oxide, acrylic acid polymers and copolymers having high swellability, acrylic acid copolymer with vinyl glycol, such as those available under the tradename Noveon®, and the like and mixtures thereof. The highly swellable polymers may be used in an amount ranging from about 0.5% to about 90% by weight of the core. Examples of superdisintegrants that can be used as the agent capable of generating internal pressure include, but are not limited to, crosslinked sodium carboxymethyl cellulose, crosslinked polyvinylpyrrolidone, sodium starch glycolate, ion exchange resins and mixtures thereof. The superdisintegrants may be used in an amount ranging from about 0.5% to about 90% by weight of the core.

The core of the gastric retention drug delivery system of the present invention may be a compressed tablet obtained by compressing an agent capable of generating internal pressure with pharmaceutically acceptable excipients, and optionally further including a therapeutically active agent, or the core may be a capsule comprising a blend of the agent capable of generating internal pressure with pharmaceutically acceptable excipients, and optionally further including a therapeutically active agent. The core may be homogenous or heterogeneous, i.e. (i) it may be a mixture of the active agent with the agent capable of generating internal pressure, wherein the mixture may be compressed, or (ii) it may be a layered core, wherein the active agent and the agent capable of generating internal pressure are present in two separate layers, wherein the layers may be laminar or concentric. A capsule or a tablet core may be obtained using conventional methods known to a person skilled in the art. Various punches and dies may be used to obtain the core, such as for example capsule-shaped, standard concave, oval, triangular and other shapes conventionally used in the pharmaceutical art.

The core of the gastric retention drug delivery system is coated with a coating composition comprising a film-forming polymer and one or more expandable components. Film-forming polymers used conventionally and known to a person skilled in the art are suitable for use in the coating composition of the present invention. Examples of film-forming polymers that may be used in the present invention include, but are not limited to, cellulose derivatives, acrylic acid polymers and copolymers, polymers of acrylic acid crosslinked with vinyl glycols and mixtures thereof. The film-forming polymer may be used in an amount ranging from about 0.5% to about 70% by weight of the coating composition.

Expandable components that may be used in the coating composition are selected from the group comprising gas generating agents, highly swellable polymers, superdisintegrants and mixtures thereof. Gas generating agents that may be used and the amounts in which they may be used are defined herein above. Examples of the highly swellable polymers that may be used in the present invention include:

- highly swellable grades of cellulose ethers such as hydroxy C<sub>1-4</sub> alkyl C<sub>1-4</sub> alkyl celluloses, carboxyalkyl celluloses, hydroxy C<sub>1-4</sub> alkyl celluloses preferably hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropyl methylcellulose, more preferably a high viscosity grade of hydroxyethylcellulose;
- gums of plant, animal, mineral or synthetic origin such as (i) agar, alginates, carrageenan, furcellaran derived from marine plants, (ii) guar gum, gum arabic, gum tragacanth, karaya gum, locust bean gum, pectin derived from terrestrial plants, (iii) microbial polysaccharides such as dextran, gellan gum, rhamsan gum, welan gum, xanthan gum, and (iv) synthetic or semi-synthetic gums such as propylene glycol alginate, hydroxypropyl guar and modified starches like sodium starch glycolate;
- acrylic acid polymers and copolymers, such as cross-linked polymer of acrylic acid with vinyl glycol and commonly known as polycarbophil, polymers available under the tradename Carbopol®, and the like;
- a vinyl pyrrolidone polymer such as crosslinked polyvinylpyrrolidone or crospovidone; copolymers of vinyl pyrrolidone and vinyl acetate; or mixtures thereof.

The highly swellable polymers may be used in an amount ranging from about 0.5% to about 40% by weight of the coating composition. Examples of superdisintegrants that may be used include, but are not limited to, cross-linked polyvinylpyrrolidone, cross-linked sodium carboxymethylcellulose, carboxymethyl starch, sodium carboxymethyl starch, potassium

methacrylate-divinylbenzene copolymer, polyvinyl alcohols, amylose, cross-linked amylose, starch derivatives, microcrystalline cellulose and cellulose derivatives, alpha-, beta-and gamma-cyclodextrin and dextrin derivatives. The superdisintegrant may be used in an amount ranging from about 0.5% to about 40% by weight of the coating composition. The core is coated to a weight gain of up to about two times the weight of the core with the coating composition. In one embodiment of the present invention, the coating is obtained by using a mixture comprising sodium starch glycolate, sodium bicarbonate, at least one acrylic acid polymer and polycarbophil.

The coating composition may further comprise pharmaceutically acceptable excipients such as channel formers selected from water soluble excipients such as mannitol, lactose, halogen salts of alkali and alkaline earth metals, and the like and mixtures thereof, in an amount ranging from about 0.5% to about 95% by weight of the coating composition; pH modifiers such as carbonate and bicarbonate salts of alkali and alkaline earth metal salts, aminosugars such as meglumine, pharmaceutically acceptable acids, and mixtures thereof, in an amount ranging from about 0.5% to about 50% by weight of the coating composition; anti-tack agents such as talc, colloidal silica and the like, in an amount ranging from about 0.5% to about 10% by weight of the coating composition; plasticisers such as Tweens, diethyl phthalate, polyethylene glycols, and the like, in an amount ranging from about 5% to about 20% by weight of the coating composition; and binders conventionally used in the art, in an amount ranging from about 0.5% to about 50% by weight of the coating composition.

Yet another embodiment of the present invention may be defined as follows :

A gastric retention drug delivery system in the form of a coated tablet comprising :

- (a) a core in the form of a tablet comprising an agent capable of generating internal pressure on the coat,
- (b) a first coating formed by coating a composition on the tablet core comprising an agent capable of generating internal pressure on the coat, and
- (c) a second coating formed by coating a composition comprising a film-forming polymer and one or more expandable components on the first coating.

The system is capable of rapidly achieving both floatation and expansion to a size suitable for retention of the system in the stomach.

One other embodiment of the present invention may be defined as follows :

A gastric retention drug delivery system in the form of a coated capsule, comprising :

- (a) a core in the form of a capsule, the core comprising an agent capable of generating internal pressure on the coating,
- (b) a first coating formed by coating a composition on the capsule core comprising an agent capable of generating internal pressure on the coat, and
- (c) a second coating formed by coating a composition comprising a film-forming polymer and one or more expandable components on the first coating.

The system is capable of achieving simultaneously the dual desirable properties of instantaneous floatation and expandability to a size suitable for retention of the system in the stomach.

The first coating, or the subcoat as it may be referred to herein, comprises an agent capable of generating internal pressure on the coat. Examples of pharmaceutical excipients that may be used as the agent capable of generating internal pressure, and the amounts in which these may be used are defined herein above. The first coating composition may further comprise a superdisintegrant selected from the group comprising crosslinked sodium carboxymethyl cellulose, crosslinked polyvinylpyrrolidone, sodium starch glycolate, ion exchange resins and mixtures thereof, in an amount ranging from about 0.5% to about 90% by weight of the coating composition. The subcoat is coated to a weight gain of about 15% to about 50% by weight of the core. In one embodiment, a mixture of alginic acid, sodium bicarbonate and sodium starch glycolate is used to obtain the subcoat. The first coating may be provided on the core by compression coating, film-coating or dry powder coating technology known to a person skilled in the art.

The outer coat is obtained by coating the tablet or capsule core with a coating composition, which is obtained by mixing the film-forming polymer and the one or more expandable components, such that the expandable component(s) is suspended in a suitable liquid vehicle. Alternatively, the core may be coated with a solution or suspension of the film-forming polymer and a dry powder coating of the one or more expandable components using known powder coating technology.

The gastric retention drug delivery system of the present invention may also include various pharmaceutically acceptable excipients, for example disintegrants such as starch, cellulose derivatives, gums, crosslinked polymers and the like; binders such as starch, gelatin, sugars, cellulose derivatives, polyvinyl pyrrolidone and the like; lubricants such as talc, magnesium stearate, calcium stearate, aluminum stearate, stearic acid, hydrogenated vegetable oils, colloidal silicon dioxide, polyethylene glycol, cellulose derivatives such as carboxyalkyl cellulose and its alkali salts, and the like; and mixtures thereof.

The gastric retention drug delivery system of the present invention rapidly swells while maintaining its physical integrity in gastrointestinal fluids and does not rupture or burst. A low density is achieved by entrapment of the gas generated by the gas generating agent such that the system floats in gastric fluids. The swelling and gas entrapment can occur rapidly such that the system is capable of achieving floatation in less than 30 minutes, preferably in less than 15 minutes, when placed in an aqueous medium. The gastric retention drug delivery system of the present invention is capable of swelling to at least twice its original volume in about 30 minutes, when placed in an aqueous medium. The outer coating is expandable in nature and retains its rigidity on expansion, thereby retaining the original shape of the device, even though the core may disintegrate. The swelling, floatation and physical integrity of the outer coat of the system together ensure and increase the time of retention of the system in the gastric milieu.

The therapeutically active agent present in the gastric retention drug delivery system of the present invention may be available in immediate release form or in modified release form, or a combination of immediate release form and modified release form. The system may comprise one or more therapeutically active agents. In case of systems that provide controlled release of the therapeutically active agent(s), a pharmaceutically acceptable release rate controlling excipient is present in admixture with the therapeutically active agent(s). The term "in admixture with" as used herein includes a physical mixture of the rate controlling excipient with the active agent in the core, as well as a rate controlling membrane covering a therapeutically active agent composition. For example, the therapeutically active agent may be in the form of controlled release multiparticulates, i.e. in the form of granules, pellets, beads or minipills comprising the therapeutically active agent in admixture with one or more release rate controlling excipients. The multiparticulates may be present in the core or in the coating of the gastric retention drug delivery system of the present invention. The multiparticulates are useful in providing independent control for release of the therapeutically active agent, and also provide isolation of the therapeutically active agent from incompatible excipients.

To summarize, the present invention is related to the following:

A1. A gastric retention drug delivery system in the form of a coated tablet comprising :

- (a) a core in the form of a tablet comprising an agent capable of generating internal pressure on the coat, and

(b) an expandable coating formed by coating a composition comprising a film-forming polymer and one or more expandable components on the tablet core.

B1. A gastric retention drug delivery system as described in A1, wherein the system further comprises one or more therapeutically active agents.

C1. A gastric retention drug delivery system as described in B1, wherein the therapeutically active agent is present in the core and the coating.

D1. A gastric retention drug delivery system as described in B1, wherein the therapeutically active agents present in the core and the coating are same or different.

E1. A gastric retention drug delivery system as described in A1, wherein the agent capable of generating internal pressure is selected from a group comprising gas generating agents, highly swellable polymers, superdisintegrants and mixtures thereof.

F1. A gastric retention drug delivery system as described in E1, wherein the agent capable of generating internal pressure is a gas generating agent selected from a group comprising carbonates, bicarbonates, sulfites, ammonium cations, sodium azide and mixtures thereof.

G1. A gastric retention drug delivery system as described in F1, wherein the gas generating agent is present in an amount ranging from about 0.5% to about 50% by weight of the core.

H1. A gastric retention drug delivery system as described in F1, wherein the agent capable of generating internal pressure is sodium bicarbonate.

I1. A gastric retention drug delivery system as described in F1, wherein the agent capable of generating internal pressure further comprises an acid source selected from a group comprising organic acids such as citric acid, malic acid, succinic acid, tartaric acid, fumaric acid, maleic acid, ascorbic acid, glutamic acid, alginic acid, acrylic acid or their salts, acrylic acid polymers and copolymers and mixtures thereof.

J1. A gastric retention drug delivery system as described in E1, wherein the agent capable of generating internal pressure is a superdisintegrant selected from a group comprising crosslinked sodium carboxymethyl cellulose, crosslinked polyvinylpyrrolidone, sodium starch glycolate, ion exchange resins and mixtures thereof.

K1. A gastric retention drug delivery system as described in J1, wherein the superdisintegrant is present in an amount ranging from about 0.5% to about 90% by weight of the core.

L1. A gastric retention drug delivery system as described in E1, wherein the agent capable of generating internal pressure is a highly swellable polymer selected from a group comprising high molecular weight polyethylene oxide, acrylic acid polymers and copolymers having high swellability, acrylic acid copolymer with vinyl glycol, and the like and mixtures thereof.

M1.A gastric retention drug delivery system as described in L1, wherein the highly swellable polymer is present in an amount ranging from about 0.5% to about 90% by weight of the core.

N1.A gastric retention drug delivery system as described in A1, wherein the coating comprises film-forming polymer selected from the group comprising cellulose derivatives, acrylic acid polymers and copolymers, polymers of acrylic acid crosslinked with vinyl glycols and mixtures thereof.

O1.A gastric retention drug delivery system as described in N1, wherein the film-forming polymer is used in an amount ranging from about 0.5% to about 70% by weight of the coating composition.

P1. A gastric retention drug delivery system as described in A1, wherein the expandable component is selected from an agent capable of generating gas, a highly swellable polymer, a superdisintegrant and mixtures thereof.

Q1. A gastric retention drug delivery system as described in P1, wherein the agent capable of generating gas is selected from a group comprising carbonates, bicarbonates, sulfites, ammonium cations, sodium azide and mixtures thereof.

R1. A gastric retention drug delivery system as described in Q1, wherein the agent capable of generating gas further comprises an acid source selected from a group comprising organic acids such as citric acid, malic acid, succinic acid, tartaric acid, fumaric acid, maleic acid, ascorbic acid, glutamic acid, alginic acid, acrylic acid or their salts, and mixtures thereof.

S1. A gastric retention drug delivery system as described in Q1, wherein the agent capable of generating gas is present in an amount ranging from about 0.5% to about 30% by weight of the coating composition.

T1. A gastric retention drug delivery system as described in Q1, wherein the agent capable of generating gas is sodium bicarbonate.

U1. A gastric retention drug delivery system as described in T1, wherein the coating further comprises alginic acid.

V1. A gastric retention drug delivery system as described in P1, wherein the highly swellable polymer is selected from a group comprising cellulose derivatives, acrylic acid polymers and copolymers, polymers of acrylic acid crosslinked with vinyl glycols and mixtures thereof.

W1. A gastric retention drug delivery system as described in V1, wherein the highly swellable polymer is present in an amount ranging from about 0.5% to about 40% by weight of the coating composition.

X1. A gastric retention drug delivery system as described in P1, wherein the superdisintegrant is selected from a group comprising crosslinked sodium carboxymethyl cellulose, crosslinked polyvinylpyrrolidone, sodium starch glycolate, ion exchange resins and mixtures thereof.

Y1. A gastric retention drug delivery system as described in X1, wherein the superdisintegrant is present in an amount ranging from about 0.5% to about 40% by weight of the coating composition.

Z1. A gastric retention drug delivery system as described in P1, wherein the expandable component is a mixture comprising at least one acrylic acid polymer, sodium starch glycolate, sodium bicarbonate, and polycarbophil.

A2. A gastric retention drug delivery system as described in A1, wherein the coating composition is coated to a weight gain of up to two times the weight of the core.

B2. A gastric retention drug delivery system as described in B1, wherein one or more therapeutically active agents is present in immediate release form to provide an immediately releasing dose of one or more of the therapeutically active agents, and modified release form to provide a modified release dose of the same or different therapeutically active agent.

C2. A gastric retention drug delivery system as described in A1, wherein the system has a floatation time of less than 30 minutes, when placed in an aqueous medium.

D2. A gastric retention drug delivery system as described in C2, wherein the system has a floatation time of less than 15 minutes, when placed in an aqueous medium.

E2. A gastric retention drug delivery system as described in A1, wherein the system is capable of swelling to at least about twice its original volume in about 30 minutes, when placed in an aqueous medium.

F2. A gastric retention drug delivery system in the form of a coated tablet comprising :

- (a) a core in the form of a tablet comprising an agent capable of generating internal pressure on the coat,
- (b) a first coating formed by coating a composition on the tablet core comprising an agent capable of generating internal pressure on the coat, and
- (c) a second coating formed by coating a composition comprising a film-forming polymer and one or more expandable components on the first coating.

G2. A gastric retention drug delivery system as described in F2, wherein the first coating composition further comprises a superdisintegrant selected from a group comprising crosslinked sodium carboxymethyl cellulose, crosslinked polyvinylpyrrolidone, sodium starch glycolate, ion exchange resins and mixtures thereof.

- H2. A gastric retention drug delivery system as described in F2, wherein the first coating composition is coated to a weight gain of about 15% to about 50% by weight of the core.
- I2. A gastric retention drug delivery system as described in F2, wherein the second coating composition is coated to a weight gain of up to two times the weight of the core coated with the first coating.
- J2. A gastric retention drug delivery system as described in F2, wherein the system further comprises one or more therapeutically active agents.
- K2. A gastric retention drug delivery system as described in A1, wherein the system further comprises a top coating comprising a film-forming polymer and a therapeutically active agent that is released immediately.
- L2. A gastric retention drug delivery system as described in A1, wherein the system further comprises a therapeutically active agent in the form of particles embedded in the coating.
- M2. A gastric retention drug delivery system as described in A1, wherein the system further comprises controlled release multiparticulates comprising one or more therapeutically active agents.
- N2. A gastric retention drug delivery system as described in M2, wherein the multiparticulates may be present in the core, in the coating or both.
- O2. A gastric retention drug delivery system as described in A1, wherein the expandable coating is such that it maintains the original shape of the system upon expansion.
- P2. A gastric retention drug delivery system in the form of a coated capsule, comprising :
- (a) a core in the form of a capsule, the core comprising an agent capable of generating internal pressure on the coating, and
  - (b) an expandable coating formed by coating a composition comprising a film-forming polymer and one or more expandable components on the capsule core.
- Q2. A gastric retention drug delivery system as described in P2, wherein the system further comprises one or more therapeutically active agent.
- R2. A gastric retention drug delivery system as described in Q2, wherein the therapeutically active agent is present in the core and the coating.
- S2. A gastric retention drug delivery system as described in Q2, wherein the therapeutically active agents present in the core and the coating are same or different.
- T2. A gastric retention drug delivery system as described in P2, wherein the agent capable of generating internal pressure is selected from a group comprising gas generating agents, highly swellable polymers, superdisintegrants and mixtures thereof.

- U2. A gastric retention drug delivery system as described in T2, wherein the agent capable of generating internal pressure is a gas generating agent selected from a group comprising carbonates, bicarbonates, sulfites, ammonium cations, sodium azide and mixtures thereof.
- V2. A gastric retention drug delivery system as described in U2, wherein the gas generating agent is present in an amount ranging from about 0.5% to about 50% by weight of the core.
- W2. A gastric retention drug delivery system as described in U2, wherein the agent capable of generating internal pressure is sodium bicarbonate.
- X2. A gastric retention drug delivery system as described in U2, wherein the agent capable of generating internal pressure further comprises an acid source selected from a group comprising organic acids such as citric acid, malic acid, succinic acid, tartaric acid, fumaric acid, maleic acid, ascorbic acid, glutamic acid, alginic acid, acrylic acid or their salts, acrylic acid polymers and copolymers and mixtures thereof.
- Y2. A gastric retention drug delivery system as described in T2, wherein the agent capable of generating internal pressure is a highly swellable polymer selected from a group comprising crosslinked sodium carboxymethyl cellulose, crosslinked polyvinylpyrrolidone, sodium starch glycolate, ion exchange resins and mixtures thereof.
- Z2. A gastric retention drug delivery system as described in Y2, wherein the highly swellable polymer is present in an amount ranging from about 0.5% to about 90% by weight of the core.
- A3. A gastric retention drug delivery system as described in P2, wherein the coating comprises film-forming polymer selected from the group comprising cellulose derivatives, acrylic acid polymers and copolymers, polymers of acrylic acid crosslinked with vinyl glycols and mixtures thereof.
- B3. A gastric retention drug delivery system as described in A3, wherein the film-forming polymer is used in an amount ranging from about 0.5% to about 70% by weight of the coating composition.
- C3. A gastric retention drug delivery system as described in P2, wherein the coating comprises an expandable component selected from an agent capable of generating gas, a highly swellable polymer, a superdisintegrant and mixtures thereof.
- D3. A gastric retention drug delivery system as described in C3, wherein the agent capable of generating gas is selected from a group comprising carbonates, bicarbonates, sulfites, ammonium cations, sodium azide and mixtures thereof.
- E3. A gastric retention drug delivery system as described in D3, wherein the agent capable of generating internal pressure further comprises an acid source selected from a group

comprising organic acids such as citric acid, malic acid, succinic acid, tartaric acid, fumaric acid, maleic acid, ascorbic acid, glutamic acid, alginic acid, acrylic acid or their salts, and mixtures thereof.

- F3. A gastric retention drug delivery system as described in D3, wherein the agent capable of generating gas is present in an amount ranging from about 0.5% to about 30% by weight of the coating composition.
- G3. A gastric retention drug delivery system as described in D3, wherein the agent capable of generating gas is sodium bicarbonate.
- H3. A gastric retention drug delivery system as described in C3, wherein the superdisintegrant is selected from a group comprising crosslinked sodium carboxymethyl cellulose, crosslinked polyvinylpyrrolidone, sodium starch glycolate, ion exchange resins and mixtures thereof.
- I3. A gastric retention drug delivery system as described in H3, wherein the superdisintegrant is present in an amount ranging from about 0.5% to about 40% by weight of the coating composition.
- J3. A gastric retention drug delivery system as described in C3, wherein the highly swellable polymer is selected from a group comprising cellulose derivatives, acrylic acid polymers and copolymers, polymers of acrylic acid crosslinked with vinyl glycols and mixtures thereof.
- K3. A gastric retention drug delivery system as described in J3, wherein the highly swellable polymer is present in an amount ranging from about 0.5% to about 40% by weight of the coating composition.
- L3. A gastric retention drug delivery system as described in C3, wherein the expandable component is a mixture comprising at least one acrylic acid polymer, sodium starch glycolate, sodium bicarbonate, and polycarbophil.
- M3. A gastric retention drug delivery system as described in P2, wherein the coating composition is coated to a weight gain of up to two times the weight of the core.
- N3. A gastric retention drug delivery system as described in Q2, wherein one or more therapeutically active agents is present in immediate release form to provide an immediately releasing dose of one or more of the therapeutically active agents, and modified release form to provide a modified release dose of the same or different therapeutically active agent.
- O3. A gastric retention drug delivery system as described in P2, wherein the system is capable of swelling to at least about twice its original volume in about 30 minutes, when placed in an aqueous medium.
- P3. A gastric retention drug delivery system in the form of a coated capsule, comprising :

- (a) a core in the form of a capsule, the core comprising an agent capable of generating internal pressure on the coating,
- (b) a first coating formed by coating a composition comprising an agent capable of generating internal pressure on the coat, and
- (c) a second expandable coating formed by coating a composition comprising a film-forming polymer and one or more expandable components on the first coating.

Q3. A gastric retention drug delivery system as described in P3, wherein the first coating composition further comprises a superdisintegrant selected from a group comprising crosslinked sodium carboxymethyl cellulose, crosslinked polyvinylpyrrolidone, sodium starch glycolate, ion exchange resins and mixtures thereof.

R3. A gastric retention drug delivery system as described in P3, wherein the first coating composition is coated to a weight gain of about 15% to about 50% by weight of the core.

S3. A gastric retention drug delivery system as described in P3, wherein the second coating composition is coated to a weight gain of up to two times the weight of the core coated with the first coating.

T3. A gastric retention drug delivery system as described in P3, wherein the system further comprises one or more therapeutically active agents.

U3. A gastric retention drug delivery system as described in P2, wherein the system further comprises a top coating comprising a film-forming polymer and a therapeutically active agent that is released immediately.

V3. A gastric retention drug delivery system as described in P2, wherein the system further comprises a therapeutically active agent in the form of particles embedded in the coating.

W3. A gastric retention drug delivery system as described in P2, wherein the system further comprises controlled release multiparticulates comprising one or more therapeutically active agents.

X3. A gastric retention drug delivery system as described in W3, wherein the multiparticulates may be present in the core, in the coating or both.

Y3. A gastric retention drug delivery system as described in P2, wherein the expandable coating is such that it maintains the original shape of the system upon swelling.

Z3. A process for preparation of a gastric retention drug delivery system in the form of a coated tablet comprising –

- (a) preparing a core in the form of a tablet comprising an agent capable of generating internal pressure on the coat, and

(b) coating the tablet core with a coating composition comprising a film-forming polymer and one or more expandable components, wherein the one or more expandable components are suspended in a suitable liquid vehicle.

A4. A process for preparation of a gastric retention drug delivery system in the form of a coated capsule comprising –

- (a) preparing a core in the form of a capsule comprising an agent capable of generating internal pressure on the coat, and
- (b) coating the capsule core with a coating composition comprising a film-forming polymer and one or more expandable components, wherein the one or more expandable components are suspended in a suitable liquid vehicle.

B4. A process for preparation of a gastric retention drug delivery system in the form of a coated tablet comprising –

- (a) preparing a core in the form of a tablet comprising an agent capable of generating internal pressure on the coat, and
- (b) coating the tablet core with an expandable coating comprising a film forming polymer which is coated in the form of a solution or suspension, and one or more expandable components that are coated in the form of a dry powder.

C4. A process for preparation of a gastric retention drug delivery system in the form of a coated capsule comprising –

- (a) preparing a core in the form of a capsule comprising an agent capable of generating internal pressure on the coat, and
- (b) coating the capsule core with an expandable coating comprising a film forming polymer which is coated in the form of a solution or suspension, and one or more expandable components that are coated in the form of a dry powder.

The examples that follow do not limit the scope of the invention and are merely used as illustrations.

### Comparative example 1

A gastric retention drug delivery system comprising metformin was obtained as mentioned in Table 1 below.

**Table 1**

Ingredients	Quantity (mg/tablet)	Quantity (% w/w)
<b>Core</b>		
Metformin hydrochloride	1000.0	81.97
Hydroxypropyl methylcellulose (HPMC E50 LV)	20.0	1.64
Polyvinylpyrrolidone (PVP K-90F)	20.0	1.64
Crospovidone	40.0	3.28
Sodium bicarbonate	15.0	1.23
Silicified microcrystalline cellulose (Prosolv SMCC 90)	100.0	8.19
Colloidal silicon dioxide	7.0	0.57
Talc	9.0	0.74
Magnesium stearate	9.0	0.74
<b>Subcoat</b>		
Alginic acid	107.81	Coated to a weight gain of about 20% by weight of the core
Sodium bicarbonate	21.56	
Sodium starch glycolate	53.9	
Mannitol SD 25	26.95	
Polyvinylpyrrolidone (PVP K-90F)	25.15	
Talc	6.47	
Tween 20	2.16	
<b>Outer coat</b>		
Eudragit L-100-55	105.78	Coated to a weight gain of about 8.5% by weight of the subcoated core
Tween 20	0.74	
Polyethylene glycol (PEG 400)	1.86	
Talc	2.97	

Metformin hydrochloride, HPMC E50LV, crospovidone and PVP K-90F were mixed and granulated using purified water. The granules thus obtained were dried, milled and mixed with sodium bicarbonate, crospovidone, Prosolv SMCC 90, colloidal silicon dioxide, talc and magnesium stearate. The blend thus obtained was compressed to obtain the core. This core was then coated with a suspension comprising alginic acid, sodium bicarbonate, sodium starch glycolate, mannitol, PVP K-90F, talc and Tween 20 in isopropyl alcohol to a weight gain of 20% by weight of the core to obtain the subcoat. This was further coated with a coating composition comprising Eudragit L-100-55, tween 20, PEG 400 and talc in isopropyl alcohol to a weight gain of about 8.5% by weight of the subcoated core.

The tablets thus obtained, when placed in 100 ml of 0.01N hydrochloric acid, did not float for up to 8 hours. The tablets also did not swell sufficiently, i.e. they were found to swell to only about 1.5 times their volume at the end of 20 hours. Thus, the tablets of this example did not possess desirable characteristics for consistent and prolonged gastric retention.

#### Comparative example 2

A gastric retention drug delivery system comprising the core as mentioned in comparative example 1, and which is coated with a subcoat as mentioned in comparative example 1, was coated with an outer coat as mentioned in Table 2 below.

**Table 2**

<b>Ingredients</b>	<b>Quantity (% w/w)</b>	
<b>Outer coat</b>		
Hydroxypropyl methylcellulose (HPMC E5)	13.04	Coated to a weight gain of about 8.5% by weight of the subcoated core
Eudragit L-100-55	73.91	
Tween 20	0.59	
PEG 400	1.49	
Talc	2.39	

The subcoated tablet was prepared as mentioned in comparative example 1 above. The outer coat was obtained by coating with a solution of HPMC E5, Eudragit L-100-55 and the coating aids in isopropyl alcohol and dichloromethane, to a weight gain of 8.5% by weight of the subcoated core.

The tablets thus obtained were evaluated as regards the time required to float, i.e. buoyancy time, and the swelling index, i.e. increase in volume of the dosage form. The results are recorded in Table 3 below.

**Table 3**

<b>Medium used</b>	<b>Buoyancy time (minutes)</b>	<b>Swelling index at the end of 30 minutes</b>
0.01N HCl	Did not float till ~7 hours	1.1
pH 4.5 buffer	Did not float till ~7 hours	1.1

The tablets did not float till about 7 hours. Small blisters were seen on the coating at the end of 30 minutes, the coating ruptured within 1 hour and gas was observed to escape in the form of bubbles. Such a coating therefore would not be suitable for a gastric retention system.

#### Example 1

A gastric retention drug delivery system comprising metformin was obtained as mentioned in Table 4 below.

Table 4

Ingredients	Quantity (mg/tablet)	Quantity (% w/w)
<b>Core</b>		
Metformin hydrochloride	750.0	81.97
Hydroxypropyl methylcellulose (HPMC E50 LV)	15.0	1.64
Polyvinylpyrrolidone (PVP K-90F)	15.0	1.64
Crospovidone	30.0	3.28
Sodium bicarbonate	11.25	1.23
Silicified microcrystalline cellulose (Prosolv SMCC 90)	75.0	8.19
Colloidal silicon dioxide	5.25	0.57
Talc	6.75	0.74
Magnesium stearate	6.75	0.74
<b>Subcoat</b>		
Alginic acid	76.00	Coated to a weight gain of about 20% by weight of the core
Sodium bicarbonate	15.30	
Sodium starch glycolate	38.00	
Mannitol SD 25	19.00	
Polyvinylpyrrolidone (PVP K-90F)	17.70	
Talc	4.50	
Tween 20	1.50	
<b>Outer coat</b>		
Noveon AA1	5.64	Coated to a weight gain of about 8.5%
Sodium bicarbonate	11.30	
Eudragit L-100-55	45.12	
Mannitol SD 25	45.12	
Sodium starch glycolate	13.16	
Tween 20	0.75	
PEG 400	1.90	
Talc	3.01	
<b>Top coat</b>		
Metformin hydrochloride	250.0	Coated to a weight gain of about 24%
Opadry YS-2-7013 Clear	35.0	

The subcoated core was obtained as mentioned in comparative example 1 above. This was further coated with a coating composition comprising Noveon AA1, sodium bicarbonate, Eudragit L-100-55, mannitol, sodium starch glycolate, Tween 20, PEG 400, talc and isopropyl alcohol to a weight gain of about 8.5% by weight. The tablets thus obtained were coated with a top coat comprising an immediate release fraction of metformin hydrochloride to a weight gain of about 24% using a coating solution comprising metformin hydrochloride and Opadry.

The coating solutions used to obtain the subcoat and the outer coat, in this and all other examples, were prepared by mixing the ingredients of the coating composition and suspending them in a

suitable carrier, stirring the mixture with an overhead stirrer, followed by introducing the mixture in a colloid mill. The mixture was milled for about 30 minutes and the dispersion so obtained was used for coating.

The tablets were subjected to dissolution studies using United States Pharmacopoeia dissolution apparatus, type II, at 50 rpm, using 1000ml of the dissolution medium. The results are recorded in Table 5 below.

Table 5

Time (hours)	Cumulative % dissolved		
	0.01N HCl	pH 3.0 buffer	pH 4.5 buffer
0	0	0	0
1	19	23	21
2	23	24	24
4	36	35	44
8	63	65	80
12	82	81	92
16	89	89	96
20	93	96	98
24	96	97	100

The tablets were evaluated as regards the time required to float, i.e. buoyancy time, and the swelling index, i.e. increase in volume of the dosage form. The tablets were introduced in 100ml of 0.01N HCl and pH 4.5 buffer to evaluate these. The swelling index of the dosage forms of the present invention was calculated as follows. The dosage form as manufactured, although a capsule or a caplet, was assumed to have the volume equivalent to a three-dimensional, solid, cylinder, i.e. the curved edges of the capsule/caplet were disregarded, and the volume was calculated accordingly. The swelling index was calculated as the increase in volume of the dosage form at the end of 30, 60, 120 and 240 minutes, assuming the swollen mass also to be a cylinder. The results are recorded in Table 6 below, wherein the buoyancy time is in minutes, and the swelling index is the number of times the volume of the dosage form increases as a function of time.

Table 6

Medium used	Buoyancy time (minutes)	Swelling index		
		30 min	60 min	120 min
0.01N HCl	33	~1.8	~2.14	~2.5
pH 3.0 buffer	27	~1.8	~1.9	~2.5
pH 4.5 buffer	12	-	~2.26	~3.15

It is therefore apparent from the above example that the composition of the outer coat significantly affects the buoyancy and the swelling index of the gastric retention drug delivery system of the present invention.

### **Example 2**

A gastric retention drug delivery system comprising a subcoated core similar to that used in example 1, was coated with an outer coating composition mentioned in Table 7 below.

**Table 7**

Ingredients	Quantity (% w/w)	
<b>Outer coat</b>		
Noveon AA1	13.46	
Eudragit L-100-55	45.28	
Mannitol SD 25	22.64	
Sodium starch glycolate	13.46	
Tween 20	0.59	
PEG 400	1.49	
Talc	2.39	
Coated to a weight gain of about 8.5% by weight of the subcoated core		

The tablets thus obtained were evaluated as regards the time required to float, i.e. buoyancy time, and the swelling index, i.e. increase in volume of the dosage form. The results are recorded in Table 8 below.

**Table 8**

Medium used	Buoyancy time (minutes)	Swelling index		
		30 min	60 min	120 min
0.01N HCl	~10-12	2.3	2.3	2.4
pH 4.5 buffer	~8-9	4	5.38	9.9

### **Example 3**

A gastric retention drug delivery system comprising a subcoated core similar to that used in example 1, was coated with an outer coating composition mentioned in Table 9 below.

**Table 9**

Ingredients	Quantity (% w/w)	
<b>Outer coat</b>		
Eudragit L-100-55	52.17	
Mannitol SD 25	26.08	
Sodium starch glycolate	15.21	
Tween 20	0.59	
PEG 400	1.49	
Talc	2.39	
Coated to a weight gain of about 8.5% by weight of the subcoated core		

The tablets thus obtained were evaluated as regards the time required to float, i.e. buoyancy time, and the swelling index, i.e. increase in volume of the dosage form. The results are recorded in Table 10 below.

**Table 10**

Medium used	Buoyancy time (minutes)	Swelling index			
		30 min	60 min	120 min	24 hours
0.01N HCl	~13-14	2.6	2.4	3	16.6
pH 4.5 buffer	~13-14	2.5	2.5	3	11.2

**Example 4**

A gastric retention drug delivery system comprising a subcoated core similar to that used in example 1, was coated with an outer coating composition mentioned in Table 11 below.

**Table 11**

Ingredients	Quantity (% w/w)	
<b>Outer coat</b>		
Noveon AA1	2.29	Coated to a weight gain of about 8.5% by weight of the subcoated core
Sodium bicarbonate	9.16	
Eudragit L-100-55	36.64	
Mannitol SD 25	36.64	
Sodium starch glycolate	10.69	
Tween 20	0.59	
PEG 400	1.49	
Talc	2.39	

The tablets thus obtained were evaluated as regards the time required to float, i.e. buoyancy time, and the swelling index, i.e. increase in volume of the dosage form. The results are recorded in Table 12 below.

**Table 12**

Medium used	Buoyancy time (minutes)	Swelling index			
		30 min	60 min	120 min	24 hours
0.01N HCl	~7	2	2.8	3.5	5.5
pH 4.5 buffer	~7	2.7	4.1	5	10.5

**Example 5**

A gastric retention drug delivery system comprising a subcoated core similar to that used in example 1, was coated with an outer coating composition mentioned in Table 13 below.

Table 13

Ingredients	Quantity (% w/w)	
<b>Outer coat</b>		
Eudragit L-100-55	40.68	Coated to a weight gain of about 8.5% by weight of the subcoated core
Sodium bicarbonate	10.17	
Sodium starch glycolate	16.95	
Mannitol SD 25	27.12	
Tween 20	0.59	
PEG 400	1.49	
Talc	2.39	

The tablets thus obtained were evaluated as regards the time required to float, i.e. buoyancy time, and the swelling index, i.e. increase in volume of the dosage form. The results are recorded in Table 14 below.

Table 14

Medium used	Buoyancy time (minutes)	Swelling index
24 hours		
0.01N HCl	~1	8.2
pH 4.5 buffer	~5-6	9.1

#### Example 6

A gastric retention drug delivery system comprising a subcoated core similar to that used in example 1, was coated with an outer coating composition mentioned in Table 15 below.

Table 15

Ingredients	Quantity (% w/w)	
<b>Outer coat</b>		
Eudragit L-100-55	33.89	Coated to a weight gain of about 8.5% by weight of the subcoated core
Hydroxypropyl methylcellulose	11.86	
Sodium bicarbonate	10.17	
Sodium starch glycolate	11.86	
Mannitol SD 25	27.12	
Tween 20	0.59	
PEG 400	1.49	
Talc	2.39	

The tablets thus obtained were evaluated as regards the time required to float, i.e. buoyancy time, and the swelling index, i.e. increase in volume of the dosage form. The results are recorded in Table 16 below.

**Table 16**

Medium used	Buoyancy time (minutes)	Swelling index		
		30 min	60 min	120 min
0.01N HCl	~6	2.6	2.7	3.6
pH 4.5 buffer	~6	2.8	2.9	3.6

**Example 7**

A gastric retention drug delivery system comprising a subcoated core similar to that used in example 1, was coated with an outer coating composition mentioned in Table 17 below.

**Table 17**

Ingredients	Quantity (% w/w)	
<b>Outer coat</b>		
Eudragit L-100-55	32.88	Coated to a weight gain of about 8.5% by weight of the subcoated core
Noveon AA1	4.11	
Sodium bicarbonate	8.22	
Sodium starch glycolate	9.59	
Mannitol SD 25	41.09	
Tween 20	0.59	
PEG 400	1.49	
Talc	2.39	

The tablets thus obtained were evaluated as regards the time required to float, i.e. buoyancy time, and the swelling index, i.e. increase in volume of the dosage form. The results are recorded in Table 18 below.

**Table 18**

Medium used	Buoyancy time (minutes)	Swelling index		
		30 min	60 min	120 min
0.01N HCl	~8-12	1.7	2.8	3.5
pH 4.5 buffer	~8-9	1.7	4.2	5

**Example 8**

A gastric retention drug delivery system comprising a subcoated core similar to that used in example 1, was coated with an outer coating composition mentioned in Table 19 below.

**Table 19**

<b>Ingredients</b>	<b>Quantity (% w/w)</b>	
<b>Outer coat</b>		
Eudragit L-100-55	40.68	Coated to a weight gain of about 8.5% by weight of the subcoated core
Noveon AA1	5.08	
Sodium bicarbonate	10.17	
Sodium starch glycolate	11.86	
Mannitol SD 25	27.12	
Tween 20	0.59	
PEG 400	1.49	
Talc	2.39	

The tablets thus obtained were evaluated as regards the time required to float, i.e. buoyancy time, and the swelling index, i.e. increase in volume of the dosage form. The results are recorded in Table 20 below.

**Table 20**

<b>Medium used</b>	<b>Buoyancy time (minutes)</b>	<b>Swelling index</b>		
		<b>30 min</b>	<b>60 min</b>	<b>120 min</b>
0.01N HCl	~8	2.8	2.5	3.3
pH 4.5 buffer	~8	3.5	3.5	5.9

**Example 9**

A gastric retention drug delivery system comprising baclofen was prepared as mentioned in Table 21 below.

**Table 21**

<b>Ingredients</b>	<b>Quantity (mg/capsule)</b>	<b>Quantity (% w/w)</b>
<b>Core</b>		
Baclofen	22.5	5.49
Fumaric acid	10.0	2.44
Mannitol SD 200	264.5	64.5
Hydroxypropyl cellulose (HXP)	68.0	16.59
Sodium bicarbonate	30.0	7.32
Colloidal silicon dioxide	5.0	1.22
Talc	5.0	1.22
Magnesium stearate	5.0	1.22
<b>Subcoat</b>		
Alginic acid	54.35	Coated to a weight gain of about 25% by weight of the core
Sodium bicarbonate	10.87	
Sodium starch glycolate	27.17	
Mannitol SD 25	13.59	
Polyvinylpyrrolidone (PVP K-90F)	16.30	
Talc	3.26	
Tween 20	1.09	
<b>Outer coat</b>		
Noveon AA1	4.41	Coated to a weight gain of about 18% by weight
Sodium bicarbonate	8.82	
Eudragit L-100-55	35.29	
Eudragit S-100	8.82	
Mannitol SD 25	35.29	
Sodium starch glycolate	10.29	
Tween 20	0.59	
Polyethylene glycol (PEG 400)	1.47	
Talc	2.35	
Diethyl phthalate	6.62	
<b>Top Coat</b>		
Baclofen	7.5	Coated to a weight gain of about 1.5%
Polyvinylpyrrolidone (Povidone K-30)	1.50	
Talc	2.25	
Tween 20	0.40	

Baclofen, fumaric acid, mannitol, hydroxypropyl cellulose, sodium bicarbonate, colloidal silicon dioxide, talc and magnesium stearate were mixed to obtain a blend and this was filled in size 0 hard gelatin capsules. The filled capsules were coated with a coating suspension containing alginic acid, sodium bicarbonate, sodium starch glycolate, mannitol, povidone, talc, Tween 20 in isopropyl alcohol to a weight gain of about 25% by weight of the core capsules. This was followed by introduction of the outer coat using a coating solution comprising Noveon AA1, sodium bicarbonate, Eudragit L-100-55, Eudragit S-100, mannitol, sodium starch glycolate,

Tween 20, PEG, talc and diethyl phthalate in isopropyl alcohol, the solution being coated to about 18% by weight. Finally, a top coat comprising baclofen, povidone K-30, talc and Tween 20 was introduced on the capsules to a weight gain of about 1.5%, using a coating solution in purified water.

The capsules thus obtained were found to float immediately upon immersion in an aqueous medium. The capsules were evaluated as regards the swelling index, i.e. increase in volume of the dosage form. The results are recorded in Table 22 below.

Table 22

Medium used	Swelling index		
	30 min	60 min	120 min
0.01N HCl	~2.12	~2.5	~3.0
pH 4.5 buffer	~2.84	~3.15	~3.53

#### Example 10

A gastric retention drug delivery system comprising carbidopa and levodopa was prepared as mentioned in Table 23 below.

Table 23

Ingredients	Quantity (mg/capsule)	Quantity (% w/w)
<b>Core</b>		
Carbidopa monohydrate	41.3	7.5
Levodopa	150.0	27.27
Fumaric acid	10.0	1.82
Mannitol SD 200	161.7	29.4
Crospovidone	25.0	4.55
Colloidal silicon dioxide	3.0	0.55
Silicified microcrystalline cellulose (Prosolv SMCC 90)	150.0	27.27
Talc	4.5	0.82
Magnesium stearate	4.5	0.82
<b>Subcoat</b>		
Alginic acid	54.35	Coated to a weight gain of about 20% by weight of the core
Sodium bicarbonate	10.87	
Sodium starch glycolate	27.17	
Mannitol SD 25	13.59	
Polyvinylpyrrolidone (PVP K-90F)	16.30	
Talc	3.26	
Tween 20	1.09	

<b>Outer coat</b>			
Noveon AA1	4.41	Coated to a weight gain of about 14.5% by weight of the core coated with the subcoat	
Sodium bicarbonate	8.82		
Eudragit L-100-55	32.35		
Eudragit S-100	2.94		
Mannitol SD 25	44.11		
Sodium starch glycolate	10.29		
Tween 20	0.59		
Polyethylene glycol (PEG 400)	1.47		
Talc	2.35		
Diethyl phthalate	5.29		
<b>Seal Coat</b>			
Opadry white YS-1-7003	Coated to a weight gain of about 3%		
<b>Top Coat</b>			
Carbidopa	12.50	Coated to a weight gain of about 11% by weight of seal coated core	
Levodopa	50.0		
Polyvinylpyrrolidone (PVP K-30)	12.50		
Talc	20.83		
Tween 20	3.33		

The coated capsules were prepared as mentioned in examples above.

### Example 11

A gastric retention drug delivery system comprising baclofen was prepared as mentioned in Table 24 below.

Table 24

Ingredients	Quantity (mg/capsule)	Quantity (% w/w)
<b>Core</b>		
Baclofen	22.5	5.49
Fumaric acid	10.0	2.44
Mannitol SD 200	200.5	48.90
Noveon AA1	108.0	26.34
Sodium bicarbonate	54.0	13.17
Colloidal silicon dioxide	5.0	1.22
Talc	5.0	1.22
Magnesium stearate	5.0	1.22

The core was obtained by blending the excipients with baclofen and filling it in a hard gelatin capsule. The capsule was then coated with a subcoat and outer coat similar to examples above.

### Example 12

A gastric retention drug delivery system comprising baclofen was obtained as mentioned in Table 25 below.

Table 25

Ingredients	Quantity (mg/tablet)	Quantity (% w/w)
<b>Core</b>		
Baclofen	22.5	3.38
Fumaric acid	10.0	1.50
Mannitol SD 200	264.50	39.77
Crospovidone	55.0	8.27
Sodium bicarbonate	30.0	4.51
Silicified microcrystalline cellulose (Prosolv SMCC 90)	253.0	38.05
Polyvinylpyrrolidone (PVP K-30)	15.0	2.26
Colloidal silicon dioxide	5.0	0.75
Talc	5.0	0.75
Magnesium stearate	5.0	0.75
<b>Seal coat</b>		
Hydroxypropyl methylcellulose (HPMC 5 cps)	20.49	Coated to a weight gain of about 3% by weight of the core
<b>Subcoat</b>		
Alginic acid	60.39	Coated to a weight gain of about 20% by weight of the seal coated core
Sodium bicarbonate	12.08	
Sodium starch glycolate	30.20	
Mannitol SD 25	15.10	
Polyvinylpyrrolidone (PVP K-90F)	18.12	
Talc	3.62	
Tween 20	1.21	
<b>Outer coat</b>		
Noveon AA1	4.00	Coated to a weight gain of about 12% by weight of the core with the seal coat and the subcoat
Sodium bicarbonate	8.00	
Eudragit L-100-55	31.99	
Eudragit S-100	8.00	
Mannitol SD 25	31.99	
Sodium starch glycolate	9.33	
Tween 20	0.53	
Polyethylene glycol (PEG 400)	1.33	
Talc	2.13	
Diethyl phthalate	4.00	
<b>Top Coat</b>		
Baclofen	7.5	Coated to a weight gain of about 1.2% by weight of the coated core
Polyvinylpyrrolidone (PVP K-30)	1.50	
Talc	2.25	
Tween 20	0.40	

The coated tablets were obtained as mentioned in examples above. The core coated with the subcoat was placed in 100ml of 0.01N HCl and pH 4.5 buffer. It was found that the subcoated tablets remained at the base of the vessel and began to disintegrate after about 3 minutes, and fully disintegrated in about 6 minutes.

The subcoated cores were coated with the outer coat and placed in 100ml of 0.01N HCl and pH 4.5 buffer. The tablets were evaluated as regards the time required to float, i.e. buoyancy time, and the swelling index, i.e. increase in volume of the dosage form. The results are recorded in Table 26 below.

Table 26

Medium used	Buoyancy time (minutes)	Swelling index			
		30 min	120 min	180 min	210 min
0.01N HCl	9	~2.44	~3.50	~3.82	~4.20
pH 4.5 buffer	9	~3.08	~4.93	~5.25	~6.77

Dated this 7<sup>th</sup> day of OCTOBER, 2004.



DILIP SHANGVI,

CHAIRMAN AND MANAGING DIRECTOR,  
SUN PHARMACEUTICAL INDUSTRIES LIMITED.